II. Claims 1-23 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious under the '532 patent in view of Coleman *et al.* (WO98/14209 [April 9, 1998]).

I. The Pending Claims are Novel Over The '532 Patent

Claims 1-3, 7-15, and 19-20 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by the '532 patent.[1] The Federal Circuit has held that "[a] claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Brothers v. Union Oil Co., of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Applicant respectfully disagrees and submits that the present claims are novel because the '532 patent fails to teach every element of the present Claims. Specifically, the art does *not* teach the coadministration of two or more antibodies or a composition of two or more antibodies.

The '532 patent describes a range of pathological conditions associated with excessive levels of NO (nitric oxide) that result from the overexpression of NO synthetase (NOS). A variety of etiologies can induce NOS overexpression (*See*, 532 patent, col. 1, lines 36-52). In particular, the '532 patent states "[i]nflammatory cytokines (e.g., TNF, interleukins or interferons) and infectious agents (e.g., endotoxin) [that] induce nitric oxide over production by inducing transcription of the inducible nitric oxide synthase gene . . . which in turn results in the over production of nitric oxide." ('532 patent, col. 2, lines 14-19). The '532 patent teaches that the prior art has attempted to treat cytokine induced overexpression of NOS by administering anti-cytokine antibodies, but that these methods have met with limited success:

> [T]here have been attempts to develop monoclonal antibodies (e.g., anti-endotoxin antibodies, anti-cytokine antibodies, anti-cytokine receptor antibodies, and the like) in efforts to block the NO production pathway at the transcriptional level. *Unfortunately, however, such efforts have met with very limited success* (see, for example, Glauser et al., in Clin. Infect. Dis. 18:S205-16 (1994) and St. John & Dorinsky, in Chest 103: 932-943 (1993)). At least one reason for the relative lack of success in the art is the fact that the production of inflammatory cytokines is short-lived (see, for example, Wange & Steinsham in Eur. J. Haematol. 50:243-249 (1993)), while over production of nitric oxide lasts several days, causing systemic hypotension, insufficient tissue perfusion and organ failure.

---

[1] The Applicant notes that Claims 4-6, 16-18, and 21-23 have not been rejected under the '532 patent.

("532 patent, col 2, lines 21-34; emphasis added). As the '532 patent teaches that anti-cytokine methods of preventing overexpression of NOS have failed, the patent therefore suggests the co-administration of 1) an agent that inhibits or inactivates a "species" that induces overexpression of NOS **and** 2) a compound that scavenge any excess NO that is produced. As such, the methods taught in the '532 patent are limited to the co-administration of these two agents.

The Applicant submits that the '532 patent does not teach even a single embodiment of the co-administration of **two** anti-cytokine antibodies, let alone the co-administration of anti-TNF-α and anti-Il-6 antibodies as recited in the presently claimed invention. The '532 patent provides only one example (*i.e.*, Example 4) that even mentions the administration of an anti-cytokine (*i.e.*, anti-TNF) antibody and never mentions co-administration of two anti-cytokine antibodies. Furthermore, example 4 provides the example of the actual co-administration of **any** two compounds, albeit **one** anti-cytokine and **one** NO scavenger, and not two anti-cytokine antibodies. However, even the lone example of co-administration of two compounds that is described in the '532 patent fails to teach that co-administration of the disclosed agents (*i.e.*, one anti-cytokine and one NO scavenger) provides improved results when compared to administration of a lone NO scavenger.

From the above, it is clear that the '532 patent does not teach methods employing two anti-cytokine antibodies (*i.e.*, anti-TNF-α and anti-IL-6 antibodies) as recited in the presently claimed invention. Thus, the Applicant respectfully requests that this rejection be withdrawn.

II. The Claims Are Non-obvious Under Coleman *et al.*

Claims 1-23 stand rejected under 35 U.S.C. §103(a) as allegedly being obviousness under the '532 patent in view of Coleman *et al.* The Applicant respectfully disagrees and submits that the Coleman *et al.* reference is not prior art. Before a reference can be considered as prior art in an obviousness rejection, the reference must qualify as prior art over the claimed invention under 35 U.S.C. §102. (*In re Bass*, 474 F.2d 1273, 177 USPQ 178 (CCPA 1973)).

As stated in the Declaration of Douglas C. Stafford (attached hereto at Appendix 2) and the supporting evidence attached thereto, the present invention was conceived and reduced

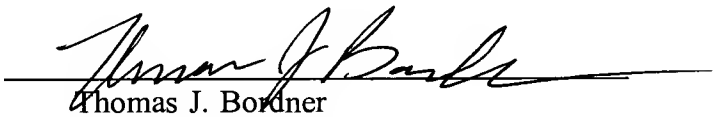
to practice prior to the publication date of the Coleman *et al.* reference. Thus, the Coleman *et al.* reference is not prior art under 35 U.S.C. §102(a). The publication date of Coleman *et al.* reference is not more than one year prior to the effective filing date of the present Application and thus, Coleman *et al.* is not prior art under 35 U.S.C. §102(b). As such, Coleman *et al.* is not available under §102(a) or (b) as prior art over the present invention and therefore the reference cannot be relied upon to form a basis for rejection under 35 U.S.C. §103(a).

Accordingly, the Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: June 7, 2001



Thomas J. Bordner
Registration No. 47,436

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104